Clinical Cancer Research

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Randomized Phase III Trial of Gefitinib versus Docetaxel in Non–Small Cell Lung Cancer Patients Who Have Previously Received Platinum-Based Chemotherapy

Dae Ho Lee[1], Keunchil Park[2], Joo Hang Kim[3], Jong-Seok Lee[6], Sang Won Shin[4], Jin-Hyoung Kang[5], Myung-Ju Ahn[2], Jin Seok Ahn[2], Cheolwon Suh[1], and Sang-We Kim[1]

Abstract

Purpose: The ISTANA (IRESSA as Second-line Therapy in Advanced NSCLC—KoreA) study compared gefitinib with docetaxel in patients with advanced or metastatic non–small cell lung carcinoma (NSCLC) pretreated with platinum-based chemotherapy.

Experimental Design: We conducted a multicenter, randomized, open-label phase III trial of gefitinib (250 mg/d) versus docetaxel (75 mg/m^2 day 1 every 3 weeks) in patients with advanced or metastatic NSCLC treated with one previous platinum-based chemotherapy. The primary endpoint was progression-free survival.

Results: A total of 161 patients (male, 62%; never smoker, 41%; adenocarcinoma, 68%) were enrolled. Progression-free survival was longer for gefitinib compared with docetaxel (hazard ratio, 0.729; 90% confidence interval, 0.533-0.998; one-sided $P = 0.0441$). Gefitinib significantly improved objective response rate (28.1% versus 7.6%; two-sided $P = 0.0007$). In the final analysis of overall survival, the hazard ratio was 0.870 (95% confidence interval, 0.613-1.236; two-sided $P = 0.4370$). No significant differences were seen in the quality of life or symptom improvement rates between the two treatment groups. Gefitinib was well tolerated, was consistent with previous data and disease, and had fewer serious adverse events and fewer Common Terminology Criteria for Adverse Events grade 3 or 4 adverse events than docetaxel. The incidence of interstitial lung disease–type events was 3.7% ($n = 3$) with gefitinib and 3.9% ($n = 3$) with docetaxel.

Conclusions: The primary endpoint of progression-free survival was longer with gefitinib than docetaxel, and the secondary endpoints showed superior objective response rate, good tolerability, and similar quality of life improvement rates for gefitinib than docetaxel. Therefore, gefitinib is an important valid treatment option for second-line therapy for Korean NSCLC patients. *Clin Cancer Res; 16(4); 1307–14. ©2010 AACR.*

Gefitinib (Iressa, AstraZeneca) is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. In phase II studies in pretreated patients with locally advanced or metastatic non–small cell lung carcinoma (NSCLC), gefitinib 250 mg/d showed clinically significant antitumor activity, as well as favorable tolerability (1, 2). A subsequent phase III study in patients with pretreated refractory NSCLC, not suitable for further chemotherapy, showed a numerical improvement in overall survival with gefitinib over placebo, although this failed to reach statistical significance in the overall study population (3). However, preplanned subgroup analyses found a significant survival advantage for gefitinib compared with placebo among patients of Asian origin and patients who had never smoked (3, 4).

Docetaxel was approved for the treatment of locally advanced or metastatic NSCLC after failure of previous platinum-based chemotherapy following two phase III studies that showed that docetaxel improved survival and quality of life compared with best supportive care (5) and with chemotherapy with vinorelbine and ifosfamide (6). However, docetaxel is associated with significant toxicity, including hematological toxicity, neurotoxicity, and asthenia.

Based on those findings, we conducted a phase III trial to compare the efficacy and safety of gefitinib with docetaxel as second-line therapy in Korean patients with locally

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Translational Relevance

This IRESSA as Second-line Therapy in Advanced NSCLC—KoreA study was the first randomized phase III study showing the advantage of molecularly targeted therapy over cytotoxic chemotherapy as second-line therapy for non–small cell lung cancer. Furthermore, the patients enrolled differed from those in Western studies in that all of them were Koreans or East Asians and 41% of them were never smokers. We have proven that a single molecular targeted agent can surpass cytotoxic chemotherapy in terms of survival outcome, as well as toxicity or quality of life.

advanced or metastatic NSCLC who had previously received platinum-based chemotherapy.

Patients and Methods

Patients. This study (IRESSA as Second-line Therapy in Advanced NSCLC—KoreA, ISTANA; study number D7913L00039) included patients with histologically or cytologically confirmed NSCLC with stage IIIB or IV disease who had received only one previous platinum-doublet chemotherapy regimen and who were considered candidates for further chemotherapy. The main inclusion criteria were age of 18 y or older, a WHO performance status of 0 to 2, progressive or recurrent disease following previous chemotherapy (adjuvant chemotherapy was allowed if full cytotoxic doses of platinum-based doublet therapy was given in patients with early disease having progressed), measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST), and adequate bone marrow, renal, and hepatic function. However, patients with previous docetaxel or any other EGFR-targeted treatment, any evidence of clinically active interstitial lung disease, newly diagnosed central nervous system metastases, or any unresolved chronic toxicity greater than National Cancer Institute Common Terminology Criteria for Adverse Events grade 2 from previous anticancer therapy were ineligible. All patients provided written informed consent before starting the study. The study was approved by Institutional Review Boards at every institution and was done in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice.

Study design. ISTANA was a randomized, open-label, parallel-group, multicentre phase III study. Eligible patients were randomly assigned to receive gefitinib or

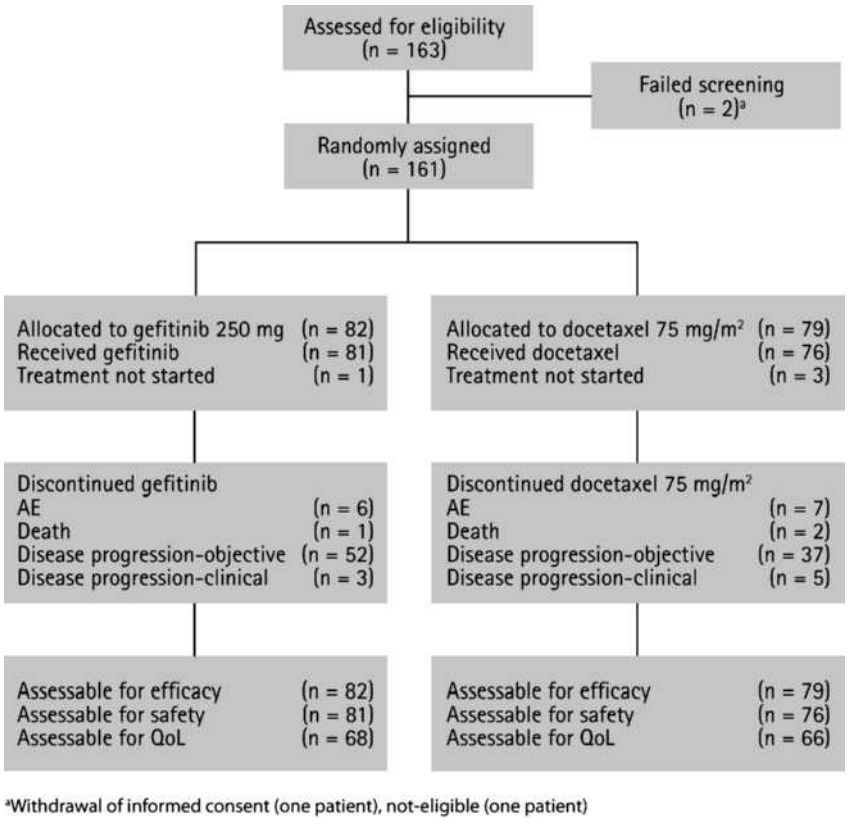

Fig. 1. Patient flow through the trial.

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Table 1. Patient demographics and disease characteristics at baseline (intent-to-treat population)

	Gefitinib (*n* = 82)	Docetaxel (*n* = 79)
Median age (range), y	57 (21-74)	58 (20-73)
Sex, *n* (%)		
Male	55 (67.1)	45 (57.0)
Female	27 (32.9)	34 (43.0)
WHO PS, *n* (%)		
0	2 (2.4)	3 (3.8)
1	74 (90.2)	71 (89.9)
2	6 (7.3)	5 (6.3)
Smoking history, *n* (%)		
Never smoker	30 (36.6)	36 (45.6)
Exsmoker	51 (62.2)	43 (54.4)
Regular smoker	1 (1.2)	0 (0.0)
Tumor histology, *n* (%)		
Adenocarcinoma	54 (65.9)	55 (69.6)
Squamous cell	17 (20.7)	11 (13.9)
Undifferentiated	7 (8.5)	9 (11.4)
Bronchioloalveolar	1 (1.2)	0 (0.0)
Mixed squamous and adenocarcinoma	1 (1.2)	1 (1.3)
Other	2 (2.4)	3 (3.8)
Best response to previous therapy, *n* (%)		
CR	0 (0.0)	0 (0.0)
PR	28 (34.1)	30 (38.0)
SD	33 (40.2)	29 (36.7)
Progression	20 (24.4)	19 (24.1)
Unknown	0 (0.0)	1 (1.3)
Nonevaluable	1 (1.2)	0 (0.0)
Disease stage		
Locally advanced	11 (13.4)	14 (17.7)
Metastatic	71 (86.6)	65 (82.3)

Abbreviations: PS, performance status; CR, complete response; PR, partial response; SD, stable disease.

docetaxel after stratification for histology (adenocarcinoma versus other), gender (male versus female), performance status (0 or 1 versus 2), best response to previous therapy (refractory versus received), smoking history (ever versus never), and participating center. Refractory to previous therapy was defined as progression on or within 3 mo of completing the previous therapy. Patients received either 250 mg/d gefitinib orally or 75 mg/m^2 docetaxel as a 1-h i.v. infusion on day 1 every 3 wk. Patients received treatment with gefitinib or docetaxel until disease progression, unacceptable toxicity, or patient's withdrawal of consent, and for docetaxel, only the maximum administration of 6 cycles was reached. For patients receiving 250 mg/d gefitinib, dose interruptions were permitted to manage toxicity, whereas for those receiving docetaxel, the dose could be reduced to 60 mg/m^2, with standard premedication administered until discontinuation of the treatment. Disease progression was to be documented radiologically using RECIST criteria. However, for patients who had convincing evidence of "clinical progression," such as worsening of performance status that was clearly cancer related but could not be documented radiologically, the decision on discontinuation of study therapy was made on a case-by-case basis following discussion with the study sponsor.

Progression-free survival was assessed from the date of randomization to the earliest date of disease progression by RECIST or death due to any cause. Tumor response by RECIST was assessed after 3 wk of each treatment and then every 6 wk. Overall survival was assessed from the date of randomization to date of death due to any cause. Changes in quality of life were assessed with the Functional Assessment of Cancer Therapy—Lung (FACT-L) questionnaire every 3 wk. From FACT-L, the following scores were calculated: the FACT-L total score, the Trial Outcome Index (sum of the physical, functional well-being, and Lung Cancer Subscale scores), and Lung Cancer Subscale score. Clinically relevant improvement was predefined as a 6-point improvement of FACT-L total score

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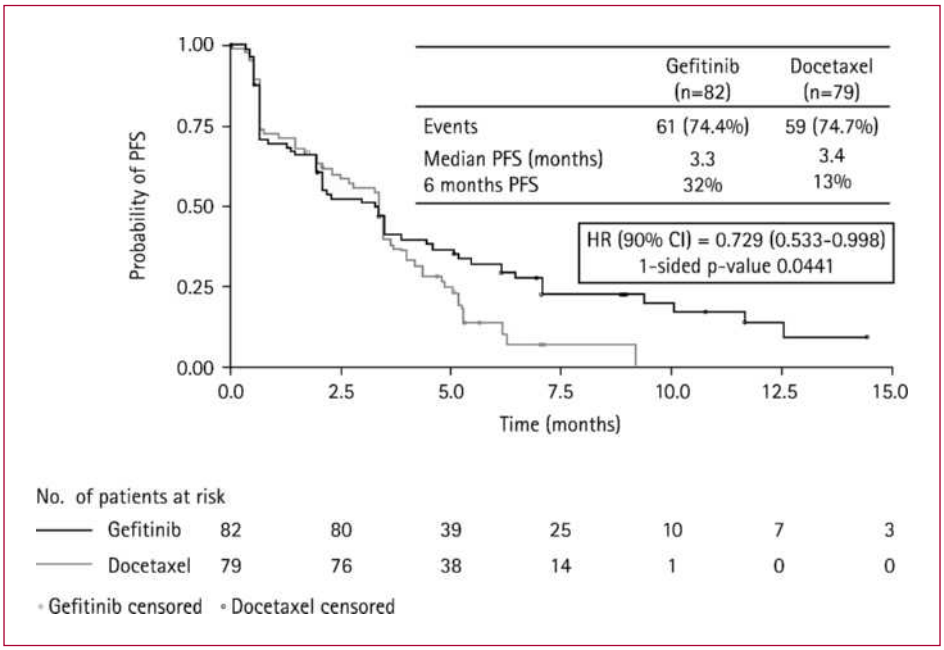

Fig. 2. Kaplan-Meier curves for progression-free survival. Primary analysis without covariates (intent-to-treat population). Hazard ratio < 1 implies a lower risk for progression on gefitinib. HR, hazard ratio; PFS, progression-free survival.

and Trial Outcome Index and 2-point improvement of Lung Cancer Subscale maintained for at least 3 wk. Adverse events were monitored and graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis. One hundred fifty patients were planned to be recruited to this trial. A total of 120 events in these patients were needed to detect superior progression-free survival for gefitinib over docetaxel using a one-sided test at the 5% significance level [90% confidence interval (90% CI)] with 80% power if the true hazard ratio was 0.63.

An unadjusted Cox proportional hazards model was used to analyze progression-free survival and overall

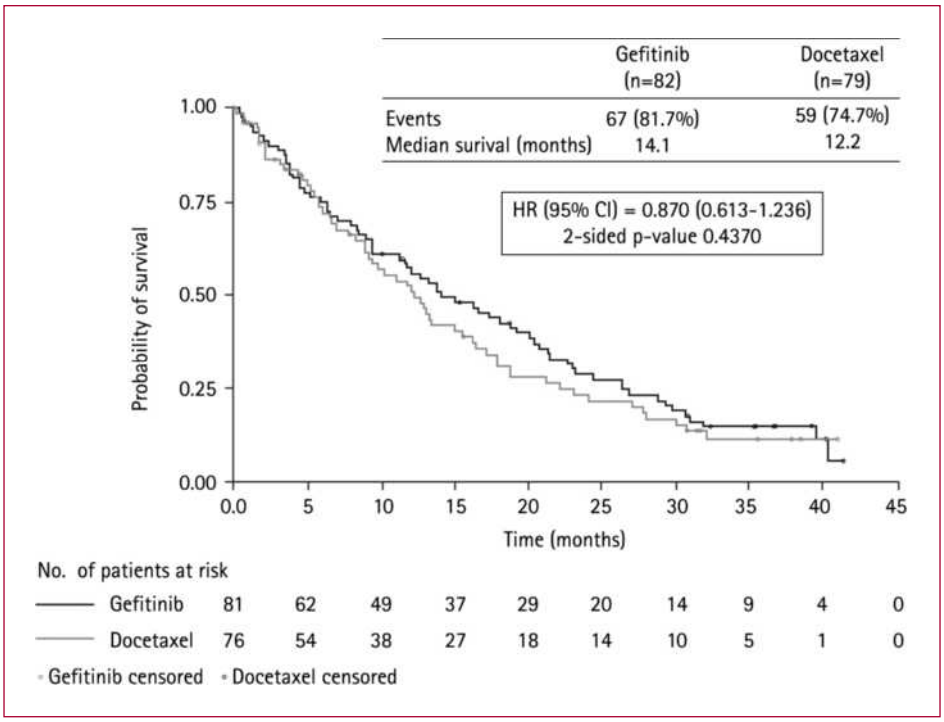

Fig. 3. Kaplan-Meier curves for overall survival. Analysis without covariates (intent-to-treat population). Hazard ratio < 1 implies a lower risk for progression on gefitinib.

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survival (two-sided test at the 5% significance level; 95% CI) to compare the treatment groups. Supportive analyses using a Cox proportional hazards model adjusting for gender, histology, smoking history, stage, and performance status were also done. Objective response rate, quality of life improvement rates, and symptom improvement were compared between the two treatment groups using the χ^2 test (two-sided test at the 5% significance level; 95% CI). All efficacy analyses were done in the intent-to-treat population. This study has been submitted for registration with ClinicalTrials.gov identifier NCT00478049.

Results

Patient characteristics. From September 2005 to September 2006, 161 patients from six centers in Korea were randomized to gefitinib (n = 82) or docetaxel (n = 79; Fig. 1). The treatment groups were well balanced for baseline characteristics (Table 1), with the exception of slightly fewer females (33% versus 43%) and never smokers (37% versus 46%) in the gefitinib treatment group than in the docetaxel group.

Efficacy endpoints. By January 2, 2007, 120 disease progressions had occurred (61 in the gefitinib treatment group and 59 in the docetaxel treatment group). Progression-free survival was found to be longer on gefitinib compared with docetaxel; the progression-free survival hazard ratio for gefitinib derived from the primary unadjusted model was 0.729 (90% CI, 0.533-0.988; one-sided P = 0.0441; Fig. 2) and from the supportive adjusted model was 0.634 (90% CI, 0.459-0.875; one-sided P = 0.0134). Median progression-free survival was 3.3 months in the gefitinib group and 3.4 months in the docetaxel group; 6-month progression-free survival rates were 32% and 13%, respectively. In terms of objective response rate (complete response plus partial response), gefitinib was statistically superior to docetaxel (28.1% versus 7.6%; P = 0.0007). A preliminary analysis of overall survival was conducted at the time of data cutoff of January 2, 2007, whereas 55 deaths had occurred (27 in the gefitinib treatment group and 28 in the docetaxel treatment group); the hazard ratio was 0.606 (95% CI, 0.350-1.049), which did not reach statistical significance. Patients continued to be followed up for survival and in the final analysis of overall survival at the time of data cutoff (February 27, 2009), whereas 126 deaths had occurred (67 in the gefitinib treatment group and 59 in the docetaxel treatment group); the hazard ratio was 0.870 (95% CI, 0.613-1.236; two-sided P = 0.4370; Fig. 3).

Quality of life and symptom improvement. Similar proportions of patients in each treatment group experienced an improvement in quality of life as measured by FACT-L total score and in lung cancer symptoms as measured by FACT-L Lung Cancer Subscale (FACT-L, 27.9% versus 27.3%, P = 0.9310; Lung Cancer Subscale, 39.7% versus 37.9%, P = 0.8282; Fig. 4). A numerical but not statistically greater proportion of patients experienced an improvement in quality of life with gefitinib than with docetaxel as measured by the Trial Outcome Index (26.5% versus 13.6%; P = 0.0641; Fig. 4).

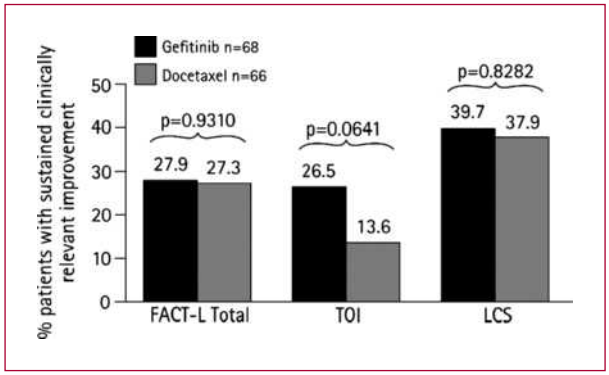

Fig. 4. Improvement rates for quality of life (evaluable for quality of life population). P values derived from χ^2 test. Clinically relevant improvement was defined as 6-point improvement for FACT-L and Trial Outcome Index and 2-point improvement for Lung Cancer Subscale maintained for ≥21 d. TOI, Trial Outcomes Index; LCS, Lung Cancer Subscale.

Safety and tolerability. Adverse events were generally mild (National Cancer Institute Common Terminology Criteria for Adverse Events grade 1 or 2) and consistent with the underlying disease and toxicity profiles previously seen with each treatment (Table 2). Serious adverse events were reported by 16% of gefitinib-treated patients and 25% of docetaxel-treated patients. There were four adverse events leading to death in the gefitinib arm (pneumonia, septic shock, interstitial lung disease; two cases, one considered possibly treatment related) and two in the docetaxel arm (pneumonia and aspiration pneumonia). The incidence of interstitial lung disease–type adverse events was 3.7% (three patients) with gefitinib and 3.9% (three patients) with docetaxel. No interstitial lung disease–type adverse events resulted in death in the docetaxel arm. Fewer dose modifications due to toxicity occurred with gefitinib (4.9% dose interruptions) than with docetaxel (17.1% dose reductions or delays).

Postdiscontinuation treatment. At the time of the final overall survival analysis (February 27, 2009), 1% patients still received randomized study treatment in the gefitinib group, whereas 24.7% received no further systemic chemotherapy apart from further EGFR tyrosine kinase inhibitor (2.5% gefitinib/erlotinib; 22.2% no treatment), 29.6% received docetaxel and 44.4% received other chemotherapy. In the docetaxel group, 26.3% patients received no further systemic therapy apart from docetaxel (1.3% docetaxel; 25.0% no treatment), 67.1% received an EGFR tyrosine kinase inhibitor, and 6.6% received other chemotherapy.

Discussion

ISTANA is the first phase III study showing an advantage of molecularly targeted therapy to cytotoxic chemotherapy

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as second-line therapy for NSCLC; gefitinib treatment showed longer progression-free survival compared with docetaxel (hazard ratio, 0.729; 90% CI, 0.533-0.998) with significantly improved objective response rate (28.1% versus 7.6%) in Korean patients.

Two recently reported phase III studies, IRESSA in NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST) and V-15-32 (comparing gefitinib with docetaxel in pretreated advanced NSCLC), have shown equivalence or similar efficacy in terms of overall survival (Table 3). INTEREST, a global study on 1,466 patients, showed noninferiority of gefitinib (250 mg/d) relative to docetaxel (75 mg/m^2 every 3 weeks) in terms of overall survival, with similar progression-free survival and objective response rate and a more favorable tolerability and quality of life profile (7). The second study, V-15-32, a Japanese study on 489 patients, failed to meet its primary objective of showing noninferiority in overall survival between gefitinib (250 mg/d) and docetaxel (60 mg/m^2 every 3 weeks) but found no significant difference between gefitinib and docetaxel in terms of overall survival and progression-free survival and superior objective response rate for gefitinib (8).

The different results of the three studies might also be derived from the different characteristics of the participating patients. ISTANA was a 100% second-line setting study, and the proportion of never smokers and responders to gefitinib were slightly higher than the other two

Table 2. Most common adverse events (those occurring in at least 10% of patients in either treatment group; evaluable-for-safety population)

n (%)	Gefitinib (*n* = 81)		Docetaxel (*n* = 76)	
	All CTC grades	CTC grade 3/4	All CTC grades	CTC grade 3/4
Gastrointestinal disorders				
Diarrhea	21 (25.9)	1 (1.2)	12 (15.8)	0 (0.0)
Nausea	13 (16.0)	0 (0.0)	14 (18.4)	0 (0.0)
Constipation	9 (11.1)	0 (0.0)	9 (11.8)	0 (0.0)
Vomiting	4 (4.9)	0 (0.0)	8 (10.5)	0 (0.0)
Stomatitis*	3 (3.7)	0 (0.0)	9 (11.8)	1 (1.3)
Dyspepsia	10 (12.3)	0 (0.0)	5 (6.6)	0 (0.0)
General disorders				
Asthenic conditions*	20 (24.7)	1 (1.2)	28 (36.8)	3 (3.9)
Chest pain	7 (8.6)	0 (0.0)	12 (15.8)	0 (0.0)
Pain	8 (9.9)	2 (2.5)	5 (6.6)	0 (0.0)
Metabolism and nutrition disorders				
Anorexia*	29 (35.8)	0 (0.0)	36 (47.4)	2 (2.6)
Musculoskeletal and connective tissue disorders				
Myalgia	4 (4.9)	0 (0.0)	29 (38.2)	0 (0.0)
Arthralgia	3 (3.7)	0 (0.0)	9 (11.8)	0 (0.0)
Nervous system disorders				
Neurotoxicity*	17 (21.0)	0 (0.0)	21 (27.6)	0 (0.0)
Dizziness	9 (11.1)	0 (0.0)	7 (9.2)	0 (0.0)
Psychiatric disorders				
Insomnia	13 (16.0)	0 (0.0)	18 (23.7)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders				
Cough	25 (30.9)	0 (0.0)	25 (32.9)	0 (0.0)
Dyspnea	20 (24.7)	3 (3.7)	21 (27.6)	3 (3.9)
Productive cough	21 (25.9)	0 (0.0)	18 (23.7)	0 (0.0)
Hemoptysis	9 (11.1)	0 (0.0)	4 (5.3)	0 (0.0)
Skin and s.c. disorders				
Rash acneiform*	61 (75.3)	3 (3.7)	6 (7.9)	0 (0.0)
Pruritus*	40 (49.4)	2 (2.5)	5 (6.6)	1 (1.3)
Alopecia	4 (4.9)	0 (0.0)	33 (43.4)	0 (0.0)
Dry skin	12 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nail and nail bed conditions*	2 (2.5)	0 (0.0)	9 (11.8)	(0.0)

Abbreviation: CTC, common toxicity criteria.
*Grouped term (sum of several preferred terms).

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Table 3. Phase III studies comparing gefitinib with docetaxel

Study	INTEREST[7] (*N* = 1,499)	V-15-32[8] (*N* = 489)	ISTANA (current; *N* = 161)
Patient characteristics, *n* (%)			
Asian ethnicity	323 (22.0)	489 (100)	161 (100)
Female	512 (34.9)	187 (38.2)	61 (37.9)
Never smoker	298 (20.3)	158 (32.3)	66 (41.0)
WHO PS 0 or 1	1,290 (88.0)	468 (95.7)	150 (93.2)
Adenocarcinoma	830 (56.6)	380 (77.7)	110 (68.3)
Responders (CR/PR) to previous chemotherapy	428 (29.2)	219 (44.8)	58 (36.0)
Second-line therapy	1,229 (83.8)	413 (84.5)	161 (100)
Treatment outcomes (gefitinib vs docetaxel)			
OS; HR, 95% CI (median); mo	1.02, 0.91-1.15* (7.6 vs 8.0)	1.12, 0.89-1.40 (11.5 vs 14.0)	0.87, 0.61-1.24 (14.1 vs 12.2)
PFS; HR, 95% CI (median); mo	1.04, 0.93-1.18 (2.2 vs 2.7)	0.90, 0.72-1.12 (2.0 vs 2.0)	0.73, 0.53-1.0† (3.3 vs 3.4)
ORR, % (*P*)	9.1 vs 7.6 (0.3257)	22.5 vs 12.8 (0.009)	28.1 vs 7.6 (0.0007)
Quality of life improvement rates (gefitinib vs docetaxel)			
FACT-L, % (*P*)	25.1 vs 14.7 (<0.0001)	23.4 vs 13.9 (0.023)	27.9 vs 27.3 (0.9310)
TOI, % (*P*)	17.3 vs 10.3 (0.0026)	20.5 vs 8.7 (0.002)	26.5 vs 13.6 (0.0641)
LCS, % (*P*)	20.4 vs 16.8 (0.1329)	22.7 vs 20.4 (0.562)	39.7 vs 37.9 (0.8282)

Abbreviations: OS, overall survival; HR, hazard ratio; PFS, progression-free survival; ORR, objective response rate; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.
*96% CI.
†90% CI.

studies. In addition, all patients in ISTANA were Korean or East Asian unlike INTEREST (Table 3). The prevalence of *EGFR* gene mutations in Korean lung cancer patients was reportedly 17.4% to 18.9%; however, it might be slightly higher than in Western countries (9–12). Because gefitinib is associated with better efficacy in never smokers who are more likely to harbor *EGFR* mutations, these differences may have driven the overall result toward superiority of gefitinib to docetaxel in terms of progression-free survival. Furthermore, the final analysis showed that gefitinib treatment showed a numerical improvement in overall survival (median survival, 14.1 versus 12.2 months) compared with docetaxel treatment, although this failed to reach statistical significance, which might be due to cross-over effect on overall survival. Early nontoxic treatment might be beneficial if there are effective treatments, which is a potential hypothesis to be assessed in a further study. In addition, IPASS study also showed that gefitinib is superior to cytotoxic chemotherapy as first-line therapy, although the patients enrolled were nonsmoker or former light smoker with adenocarcinoma histology, as well as East Asians (13).

Some may highlight the following potential limitations of our study: 1) its primary endpoint was progression-free survival; 2) its sample size was smaller than other similar studies; and 3) its study population was selected (only Korean or Asian ethnicity patients and a higher proportion of never smokers and patients with adenocarcinoma histology). However, progression-free survival is a clinically meaningful endpoint that represents a direct benefit to the patient and is largely unaffected by postdiscontinuation therapies, which have complicated the interpretation of survival data in other similar studies in this setting. The sample size was relatively small; however, an advantage for gefitinib over docetaxel in the primary progression-free survival endpoint was still shown. Compared with INTEREST, the proportion of never smokers and patients with adenocarcinoma histology was higher, and all patients were Korean, which might have translated into the higher response. However, considering that the patients were broadly representative of a pretreated advanced NSCLC study population in Korea (14, 15) and patient characteristics were well balanced in the two treatment groups (with the exception of never-smoking status, which tended to be slightly lower in the gefitinib-treated group; 37% versus 46%), the study is likely to represent the true effect of gefitinib versus docetaxel in Korean patients.

Before ISTANA was commenced, we decided not to assess biomarkers because the sample numbers might be too small to reach any robust conclusions, given that we expected tissue samples might be available only in <30% to 40% of patients enrolled. In addition, *EGFR* gene mutation or amplification has not yet been confirmed to be a

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predictive marker of overall survival for gefitinib versus docetaxel.

Lastly, we did not find any statistically significant difference in quality of life improvement rates assessed by FACT-L total score, Trial Outcome Index, and Lung Cancer Subscale, which might be partly because of the small sample size. However, improvement of physical or functional well-being domain was prominent in gefitinib-treated patients (reflected in Trial Outcome Index), but improvement of Lung Cancer Subscale domain was similar, which is consistent with the other two studies (7, 8). Unlike them, more patients with improvement of social/familial and emotional well-being domains was observed in docetaxel-treated patients (data not presented), which should be studied further. Adverse events in our study were consistent with those previously reported. Gefitinib was associated with rash acneiform, pruritus, rash, and diarrhea, whereas docetaxel was associated with alopecia and myalgia. Although the hematologic toxicity was rather infrequent in the docetaxel treatment group, this might be due to infrequent examinations, meaning measurements were not taken at the nadir.

In conclusion, gefitinib showed an advantage over docetaxel in terms of progression-free survival and objective response rate in Korean patients as second-line treatment, and should be considered a preferred treatment option in this clinical setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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